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# Docking studies of (-)-Epigallocatechin-3-gallate: A Potential Non-Competitive Pancreatic Lipase Inhibitor.

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**ABSTRACT**

(-)-Epigallocatechin-3-gallate (EGCG) a natural compound presented in the green tee was detected as potent pancreatic lipase (PL) inhibitors, according to a non-competitive mode. However, the binding mode of this Catechin into the pancreatic lipase (PL) is unclear. In order to propose a plausible mechanism between EGCG and PL, we performed a docking simulation using Molegro Virtual Docker. It revealed that the cavity 3 situated in the vicinage of site active presented the preference pocket of binding for EGCG in both porcine and human pancreatic lipase (PPL and HPL), which is stabilized by strong non-covalent bond leading to a change in geometry of active site. Five hydrogen bonds were detected between EGCG and PPL with residues: Asp 206, Gln 239, Leu 214, and His 264, in which the last residue belong to the catalytic triad. As for human pancreatic lipase, nine strong hydrogen bonds are observed with residues: Asn 212, Leu213, Asp205, Cys261, Phe258, Lys238, Lys239, and His263, which proved a better affinity of EGCG to HPL than PPL lipase. The orientations of the EGCG in the PPL and HPL, respectively, were explained by a comparison study. EGCG has better inhibitory activity against HPL compared to the PPL.

**Keywords**: EGCG, Non-competitive, Pancreatic lipase, Docking simulation, Inhibition.

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## INTRODUCTION

On a global scale, obesity has reached epidemic proportions and is a major contributor to the global burden of chronic disease and disability [1]. Recent reports showed that there are more than one billion over-weight adults worldwide including at least 300 million classified as clinically obese [2]. Several pathological disorders are associated with obesity, such as diabetes, arteriosclerosis, cardiovascular disorders, musculoskeletal disorders and some types of cancer [3,4]. Different types of anti-obesity drugs were developed and some were inappropriate in the market. One of these is orlistat (Xenical), which decreases intestinal absorption of fat via inhibition of pancreatic lipase (PL) .Others such as sibutramine, an appetite suppressant, has been associated with increased cardiovascular events and strokes and has been withdrawn from the market in several countries [5].

Lipases are important enzymes for lipid absorption. Fat absorption or obesity can be controlled by inhibition of lipases. Pancreatic lipase (PL) is a key lipase, responsible for the hydrolysis of 50-70% of total dietary fats. Reducing fat absorption with a PL inhibitor can reduce obesity [6]**.** At present, the potential of natural products for the treatment of obesity is still largely unexplored and might be an excellent alternative strategy for the development of safe and effective anti-obesity drugs [7]**.** Green tea has attracted attention of researchers because of its health advantages to a diversity of disorders, ranging from cancer to weight loss. Epigallocatechin gallate (EGCG) is the best studied and most abundant of the tea catechins, accounting for 50-80% of the total catechin content. This represents 200-300 mg per cup of brewed green tea [8]. EGCG possesses arrange of biological and medicinal properties, including antioxidant, anti-carcinogen, anti-obesity, antibacterial, antiviral and anti-enzymatic effects and anti-metastasis [9]. However, the inhibitory mechanism of this substance on PL remains unclear. It was generally attributed to the ability of tannins to bind, complex and precipitate proteins although some studies reported non-competitive or mixed inhibitions of PL [10]**.**

Kinetics findings for lipase demonstrated that EGCG inhibition of lipase was non competitive, therefore, EGCG inhibited porcine lipase activities by not binding the catalytic sites of lipase. The thermodynamic parameters suggested that the interaction was spontaneous, with hydrogen bonds and an electrostatic force perhaps primarily responsible for the interaction, CD studies indicated conformation change of lipase on binding to EGCG [11]**.** The detailed interaction nature between EGCG with PL, was determined by docking, this technique is a term used for computational schemes that attempt to find the best matching between two molecules: a receptor and ligand [12], which has a special place in design and drug discovery as well as in studies of the mechanism of action of pharmacologically active molecules [13]**.**

Consequently, in current work we used the molecular docking in order to understand and characterize the binding interaction of (-)-Epigallocatechin-3-gallate (EGCG) and PL. The present study helps in explain the mechanism of action of EGCG as hypolipidemic agent. It can also give new insights toward the binding interactions of Catechin with PL which can guide to the screening and discovery of new natural PL inhibitors. For this purpose, human and porcine pancreatic lipases have been used in this study.

## METHOD AND MATERIAL

### Protein structure and ligand

The crystal structure of each target pancreatic lipase (human and porcine) used in this study, was retrieved from the Protein Data Bank (PDB) at the Research Collaboratory for Structural Bioinformatics (RCSB, http://www.rcsb.org). The two selected PDB IDs is (1ETH) and (1LPB) represent the crystal structures of PPL and HPL, with resolution of 2.8 Å and 2.46 Å, respectively. **Whereas** the 3D structures of EGCG ligand (CID: 65064) was downloaded from PubChem (http://pubchem.ncbi.nlm.nih.gov/) and 2D structure of the EGCG is drawn using ACD/ChemSketch software (Figure 1).

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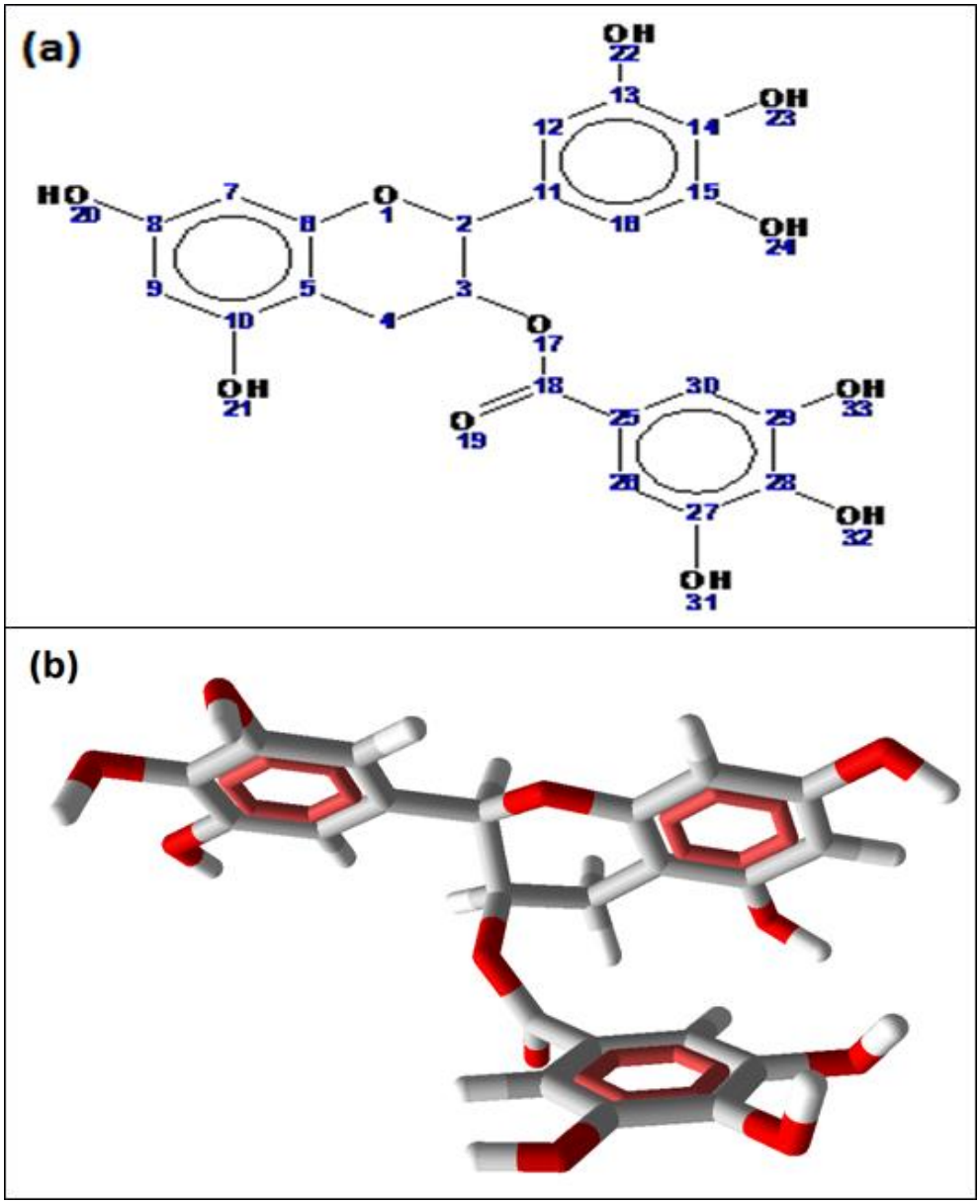


**Figure 1. The 2D (a) and 3D (b) structure of EGCG for molecular docking study.**

**Molecular docking study**

The docking of the (-)-Epigallocatechin-3-gallate into each lipase was performed using the Molegro Virtual Docker (MVD 2012.5.5.0, Molegro ApS). The accuracy of MVD is higher, compared with the other dock softwares such as Glide, Surflex, and FlexX [14].

Molegro Virtual Docker is a docking analysis tool used to predict protein-ligand interactions. It based on a novel search algorithm that combines differential evolution with a cavity prediction algorithm [15]. Water molecules, cofactors, and ions were excluded; the protonation states (ligands and protein) were set to the physiological pH; the rotatable bonds of the ligands were set to be free, and the enzyme was treated as a rigid body while docking [16]. The binding pocket was defined using the MVD cavity detection algorithm and the scoring function used was MolDock Score and PLANTS Score to evaluate the docking solutions. The MolDock scoring function (MolDock Score) used by MVD is based on a piecewise linear potential (PLP), this scoring function is originally proposed by Gehlhaar et al [17, 18], and later completed by Yang et al [19].

The MolDock Score docking scoring function, $E_{\text{MolDock Score}}$, is defined by the following energy terms (Eq. 1):

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$$E_{MolDockScore} = E_{inter} + E_{intra} \quad (1)$$

Where, $E_{inter}$ represents the ligand-protein interaction energy (Eq. 2):

$$E_{inter} = \sum_{i \in ligand} \sum_{j \in protein} \left[ E_{PLP}(r_{ij}) + 332.0 \frac{q_i q_j}{4r^2_{ij}} \right] \quad (2)$$

Where, $E_{PLP}$ is the piecewise linear potential, the numerical value of 332.0 fixes the units of the electrostatic energy in kcal/mol. The second term describes the electrostatic interactions between charged atoms, and the internal energy of the ligand ($E_{intra}$) is expressed by Eq. 3:

$$E_{intra} = \sum_{i \in ligand} \sum_{j \in ligand} E_{PLP}(r_{ij}) + \sum_{flexiblebonds} A[1 - \cos(m.\theta - \theta_0)] + E_{clash} \quad (3)$$

The double summation contains all atom pairs in the ligand except those which are connected with two bonds or less. Second term is a torsional energy where θ is the torsional angle of the bond. $E_{clash}$ assigns penalty of 1000 provided that the distance between two heavy atoms is less than 2.0 Å [20].

Moreover, the PLANTS scoring function ($E_{plantscore}$) used by MVD is defined by the following energy (Eq. 4):

$$E_{plantscore} = f_{PLP} + f_{clash} + f_{tors} + f_{site} - 20 \quad (4)$$

The PLP potential is similar to the one used by MolDock Score, but with PLANTS Score, more types of interactions (repulsive, buried, nonpolar, hydrogen bonding and metal) are better evaluated. Additionally, the ligand clash and torsional potentials, $f_{clash}$ and $f_{tors}$, take into account internal ligand clashes and torsional contributions for the flexible bonds in the ligand. $f_{site}$ therm, specifies a penalty calculated when a ligand conformation (pose) is located outside the binding site [21]. MVD returns multiple poses representing different potential binding modes. Here, clustering has been used to reduce the number of poses found during the docking run and only the most promising ones was reported [22].The docking sphere was centered to the detected cavity and the radius set to 9 Å. The present docking study was carried out using the following search algorithms: MolDock optimizer, MolDock SE (MSE), and Iterated Simplex (Simplex) as implemented in MVD. Their parameter settings are illustrated in table 1.

**Table 1. The optimizer values used while docking were expressed by the parameter settings of search algorithms above mentioned.**

| *Search algorithm* | *MolDock optimizer* | *MolDock SE* | *Simplex* |
|---|---|---|---|
| *Population size* | 50 | 50 | 20 |
| *Max iterations* | 2000 | 1500 | 100 |
| *Scaling factor* | 0.5 | - | - |
| *Crossover rat* | 0.9 | - | - |
| *Energy threshold* | - | 100 | - |

The number of runs is set to 30 in this work. Poses were constrained to the detected cavity and H-bonds are optimized after each pose prediction; this procedure can significantly reduce the number of unlikely hydrogen bonds. In the docking simulations with MVD, the pose with the minimum MolDock score value was selected as the best solution, and for creating two dimensional representations of interactions between ligand and enzyme, LigPlot+ software was used [23].

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## RESULTS AND DISCUSSION

### Docking of (–)-Epigallocatechin-3-gallate (EGCG) into PPL

The structure of protein was loaded on to MVD platform for finding potential active sites or cavities. A total of eight cavities were detected in the protein by using Molegro Virtual Docker cavity prediction with a grid resolution of 0.8 Å. An analysis of cavities displayed (Figure 2), and revealed that the binding pocket **1** is the principal cavity which is surrounded by the catalytic triad (Ser 153 - Asp 177 - His 264). The predicted pocket is located in a large N-terminal domain showing a typical α/β hydrolase fold dominated by a central parallel β-sheet.

Firstly, the docking into cavities situated more far the active site is not considered, because far interaction between ligand-enzyme cannot modify the geometry of catalytic site. Table 2 summarized the docking results of the complex ligand/PPL into the four selected cavities (2, 3, 4 and 7). The best Dock score and low bound energy is attributed to the best pose.

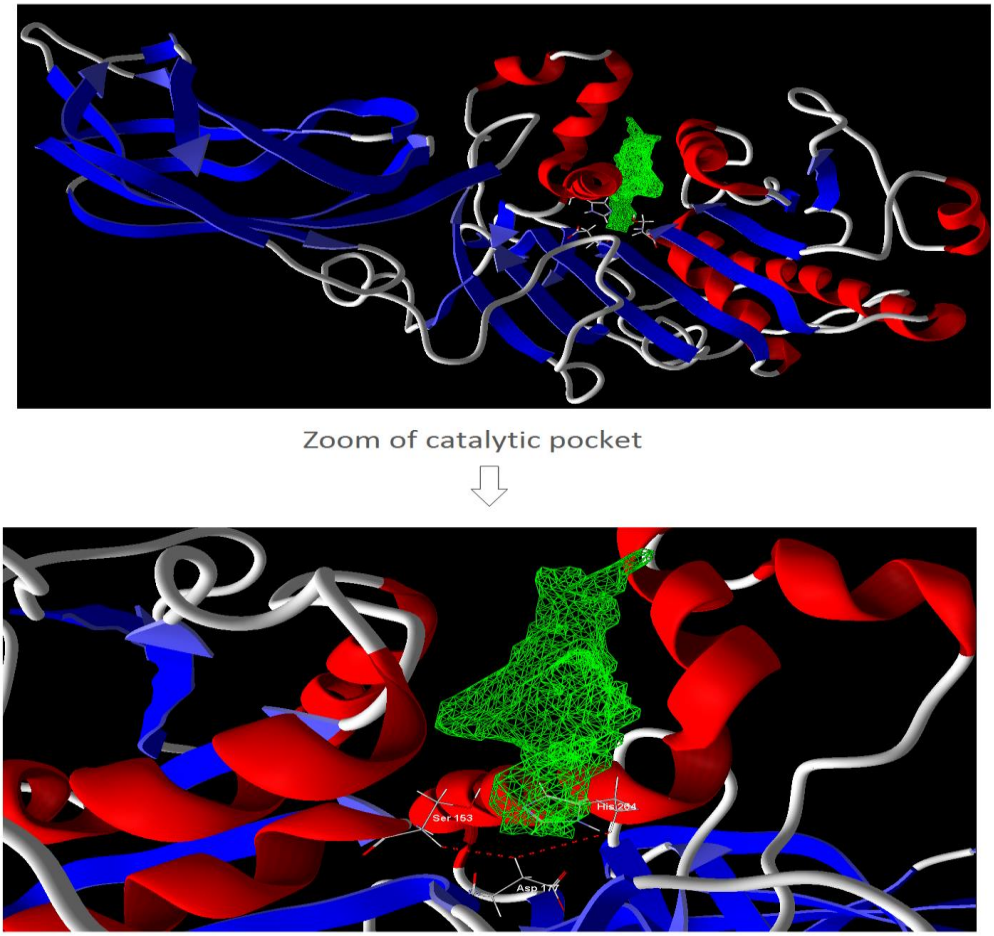


**Figure 2. Porcine pancreatic lipase (PDB: 1ETH) with catalytic pocket and its important residues. Helices are shown in red, sheets in blue and loops in grey.**

**Table 2. MolDock Score, Rerank Score and H-Bond Score results generated from MVD docking of ligand into the probable cavities (2, 3, 4 and 7).**

| *Cavities* | *MolDock Score* | *Rerank Score* | *H-Bond Score* |
|---|---|---|---|
| 2 | -128.46 | -91.28 | -17.27 |
| 3 | **-139.69** | **-115.21** | -13.43 |
| 4 | -112.04 | -87.66 | -24.11 |
| 7 | -128.29 | -98.47 | -12.24 |

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According to docking result, the less significant energy is generated with the probable cavity 4, based on MolDock score (-112.04 kcal $mol^{-1}$) and Rerank score (-87.66 kcal $mol^{-1}$). As illustrated in figure 3, it is clearly showed that this binding pocket is situated so far from the principal cavity (23.14 Å), the spontaneous interaction with hydrogen bond and electrostatic interaction between EGCG and PPL, cannot alter the molecular conformation of lipase. As a result, the enzyme catalytic activity is decreased.

Although the cavity 7, the cavity number 2 is more close to the principal active site (8.47 Å), however the result of docking in that cavity did not gives significant values of energies, it was probably attributed to the incompatibility of the shape and volume of this pocket with the size of inhibitor.

Interestingly, the best result is obtained with the probable cavity 3, where the predicted pose (EGCG) is bound to PPL with affinity of -139.69 kcal $mol^{-1}$ and -115.21 kcal $mol^{-1}$ based on MolDock score and Reranck score, respectively. It should be noted that, this cavity is located at the vicinity of active site (8.54 Å), it is surrounded by several Helices α, and so the fixation of the inhibitor in this pocket decreases significantly its energy value.

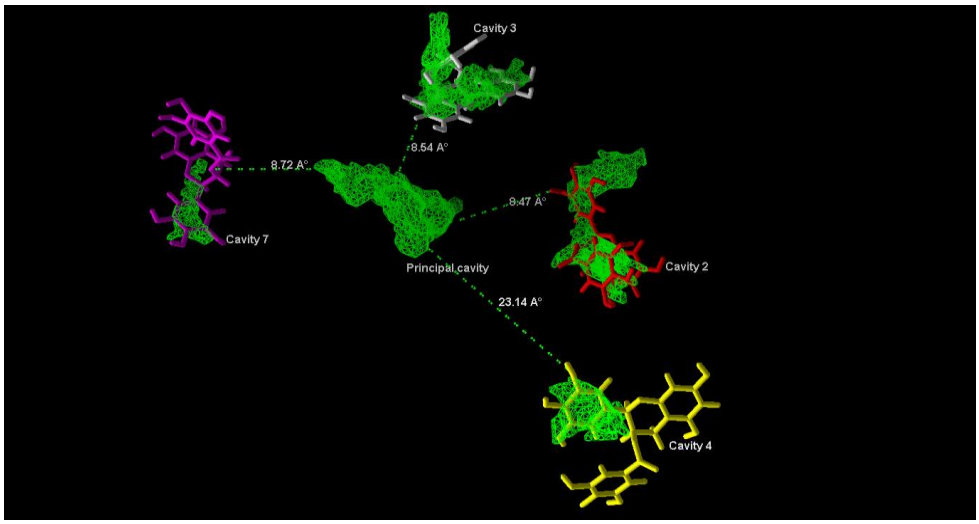


**Figure 3. Orientation of best docking poses of EGCG into the PPL binding sites (2, 3, 4, and 7) obtained by MVD programs. The green grids represent cavities of the PPL.**

The obtained results suggest that the better binding pocket site for the Epigallocatechin-3-gallate/PPL complex is the cavity 3 since it gave better performance result. So, in order to improve this suggestion, we have preferred to achieve our study by employing another score functions and algorithms as available MVD. To estimate the binding affinity and orientation of the ligand into the selected cavities, we have performed an MVD calculation using the following score functions (MolDock score, Plant score) and algorithms (SE, Simplex, Optimizer). The docking results are summarized in table 3.

**Table 3. MolDock score, Rerank score and H-Bond score results generated from MVD docking using (MolDock score, Plant score) functions and (SE, Simplex, Optimizer) algorithms.**

| ***Score Function*** | ***Algorithms*** | ***Binding Affinity*** | | | |
|---|---|---|---|---|---|
| *MolDock Score Grid* | SE | ***Cavity*** | ***MolDock-Score*** | ***Reranck-Score*** | ***HBond-Score*** |
| | | 2 | -128.75 | -90.90 | -17.60 |
| | | 3 | **-139.15** | -115.01 | -17.28 |
| | | 4 | -104.38 | -85.61 | -17.45 |
| | | 7 | -128.35 | -94.21 | -10.72 |
| *MolDock Score Grid* | Simplex | ***Cavity*** | ***MolDock-Score*** | ***Reranck-Score*** | ***HBond-Score*** |
| | | 2 | -128.31 | -91.29 | -17.69 |
| | | 3 | **-139.55** | -114.92 | -13.40 |
| | | 4 | -111.86 | -87.49 | -24.23 |
| | | 7 | -130.27 | -98.85 | -12.34 |

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| *Plant Score Grid* | Optimizer | ***Cavity*** | ***Plant-Score*** |
|---|---|---|---|
| | | 1 | -65.79 |
| | | 3 | **-72.23** |
| | | 4 | -67.45 |
| | | 7 | -65.39 |
| *Plant Score* | Optimizer | ***Cavity*** | ***Plant-Score*** |
| | | 2 | -55.81 |
| | | 3 | **-74.82** |
| | | 4 | -65.68 |
| | | 7 | -67.14 |

According to the results (table 3), an almost similar behavior of energy affinity value was found with all performed docking calculations, the Epigallocatechin-3-gallate (EGCG) share the same binding pocket previously determined (cavity 3). We have substantiated the results obtained from the docking studies (Figure 4) with the CD results in which the EGCG might disturb the α-helices around the catalytic site and therefore destabilize the catalytic site to some degree [24].

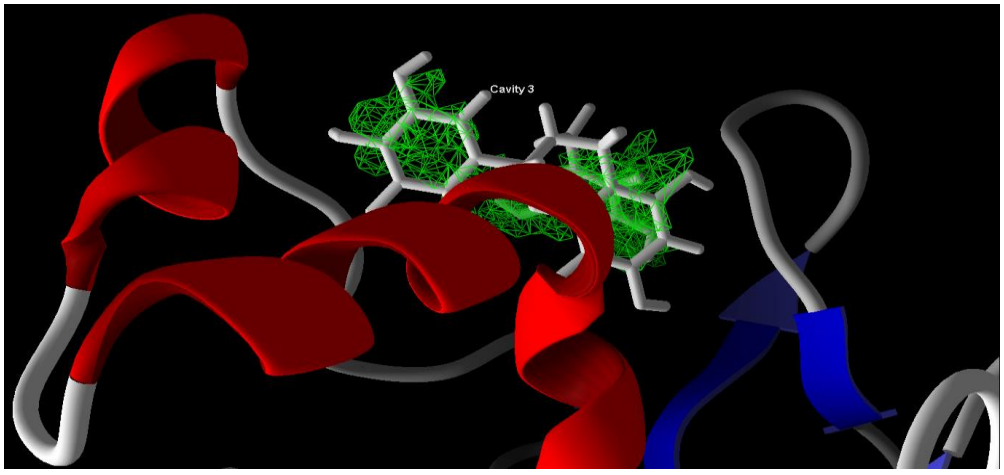


**Figure 4. Binding orientation of Epigallocatechin-3-gallate (EGCG) in the best EGCG/1ETH solution. Ligand is shown as stick model, enzyme as secondary structure backbone.**

The results of docking study have inferred that compound EGCG was found to possess five putative hydrogen bonds with binding sites of protein as shown by blue dotted lines (Figure 5). It has been observed that important hydrogen bond was formed between Hydroxyl group at position (20) and a residue of the catalytic triad His 264 (O20–N: d=2.59 Å). The other hydrogen bonds detected between the EGCG and PPL are: EGCG–O21 and Leu 214–CO (O21–O: d=2.56 Å); EGCG–O22 and Gln 245 (O22–N: d=2.78 Å); EGCG–O33 and Asp 206-OH (O33–O: d=2.58Å); EGCG–O20 and Asp 206–OH (O20–N: d=3.09 Å).

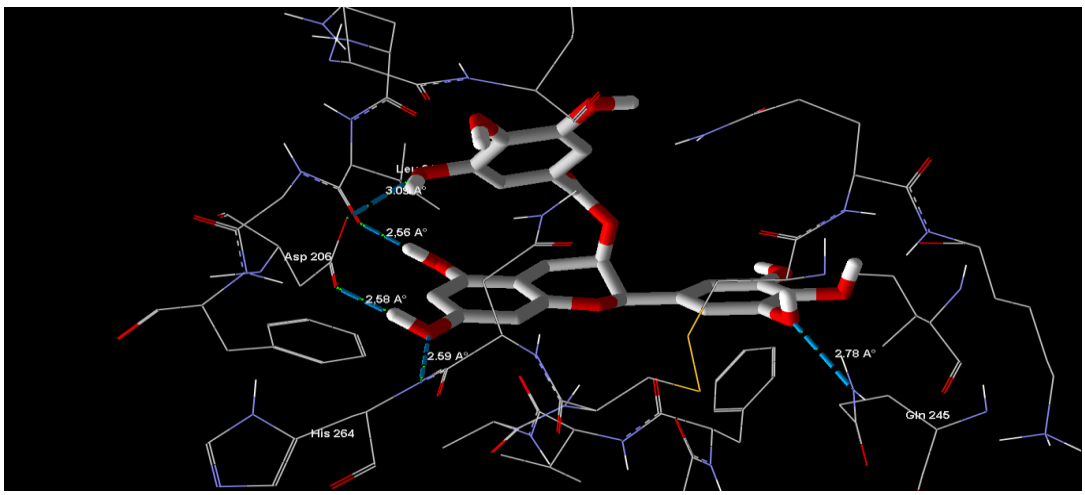

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**Figure 5. Hydrogen bonding interactions between LPP receptor and EGCG represented in green dotted lines.**

In addition to H-bond, a hydrophobic interaction was detected between EGCG and the amino acids (Val 260; Leu 214 and Ile 242). Another significant interaction than aromatic π–π stacking, was observed between the EGCG and aromatic residues (Phe 216, Phe 259) (Figure 6).

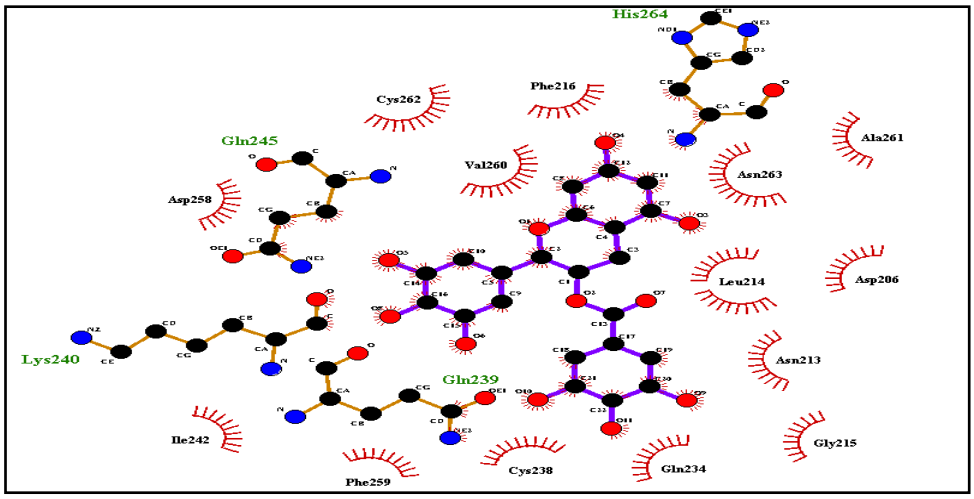


**Figure 6. Hydrophobic interaction between EGCG and PPL produced by program LIGPLOT+. The red spikes on the arcs show the hydrophobic interaction with the amino acids presented in black.**

In the light of the previous docking calculations, it can be assumed that MolDock score function provides accurate characterization of non-bonded interactions responsible of EGCG/PPL stability.

**Docking of (−)-Epigallocatechin-3-gallate (EGCG) into HPL**

In order to gain insight into the plausible mechanism of action in vivo, docking simulations were performed using Human Pancreatic Lipase (HPL). This lipase is a monomeric glycoprotein, composed of 449 amino acids, which are divided into two distinct domains: a larger N-terminal domain comprising residues 1–336 and a smaller C-terminal domain made up of residues 337- 449 (Figure 7**)** [25].

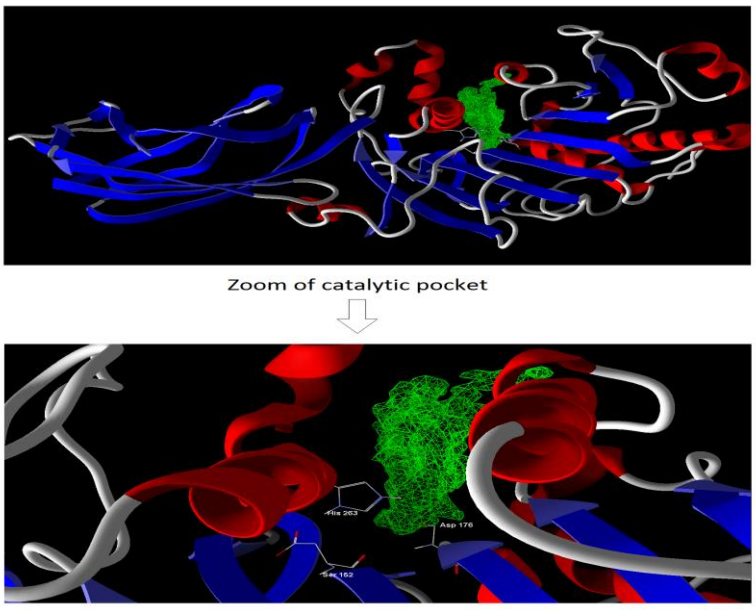


**Figure 7. Secondary structure of Human pancreatic lipase (PDB: 1LPB) with catalytic pocket and its important residues. Helices are shown in red, sheets in blue and loops in Gray.**

Catalytic triad (Ser152 – Asp176 – His 263) of HPL, and the lid in the two domains (3D structure) are located in a large N-terminal domain showing a typical α/β hydrolase fold that are dominated by a central parallel β-sheet [26].

Molecular Docking study of HPL is carried out by MolDock algorithm because it showed fast and better overall performance in docking simulations when compared with other functions (table 2). The entire enzyme structure was loaded on to MVD platform for finding potential cavities. A total of five cavities were detected in modeled HPL, where the docking study has been conducted with the same protocols used previously.

MethoxyUndecylphosphinic ACID (MUP) is bonded to the enzyme in the structures of complexes 1LPB. Therefore, in those cases the characterization of active site is easy, because the binding site occupied by the competitive inhibitor presented the catalytic site (cavity 1). As well as the visualization of the amino acid that surrounds cavities confirms that the cavity 1 presents the active site.

Docking study has been achieved with human lipase pancreas in which two cavities (2 and 3), situated near the active site, were selected in the MolDock GRID for docking simulations. Table 4 reported the calculated values of affinity energy obtained for the best pose solution.

**Table 4. MolDock Score, Rerank Score and H-Bond Score values for EGCG/HPL generated from MVD docking using MolDock score function.**

| *Cavities* | *MolDock score* | *Rerank score* | *H-Bond score* |
|---|---|---|---|
| 2 | -122.20 | -94.17 | -13.88 |
| 3 | **-157.25** | -128.24 | -21.56 |

In the case of HPL enzyme and compared to cavity 2, the best binding pocket is attributed to cavity 3 which reveals an important docking score of about -157.25 kcal $mol^{-1}$.

**Interactions between EGCG and HPL in the EGCG/1LPB complex**

We analyzed the interactions between EGCG and the HPL in the EGCG/1LPB complex from MVD using the LPC/CSU server. These complexes showed several putative non-bonding interactions between EGCG and the residues of the HPL, including hydrogen bonding, π–π stacking, hydrophobic, and van der Waals.

Figure 8 displayed nine hydrogen bonds established between ligand (EGCG) and Lipase pancreas human. The hydroxyl group at position 32 forms two hydrogen bonds, one with Asp205 (O32—N: d=2.61 Å) and the second with Phe215 (O32—O: d=3.29 Å). Another H-bond interaction between Oxygen of oxane ring and the residue Lys 238(O1—N) is formed with a distance of 3.20 Å, the carbonyl group of Lys239 forms H-bond interaction with ligand (O23—O) where interspatial distance is about 3.20 A°. Also one hydrogen bond is observed between the residue Asn212 and EGCG (O20—O: d=3.03 Å), the following two hydrogen bonds has been occurred between (Cys261, Phe285) and the carbonyl group of galloyl ester with a distance of 2.84 Å; 3.01 Å respectively. Hydroxyl group at position (31) of EGCG moiety bonded with Leu 213 (O31—O: 2.71 Å). Finally a key hydrogen bond was detected between the epigallocatechin-3-gallate and the residue His 263(O33—N: d=2.59 Å), which forms part of the catalytic triad.

The docking studies of the EGCG showed that these complexes interact also by hydrophobic contacts to HPL. There are four important hydrophobic contacts between the EGCG atoms and Ile 241, Leu 213, Ala 259, Gly 214, and Lys 132 amino acids, as shown in figure 9. Also, there are two π–π stacking (face-to-face aromatic–aromatic) interactions detected between the EGCG rings and the aromatics residues (Phe 215, Phe 258).

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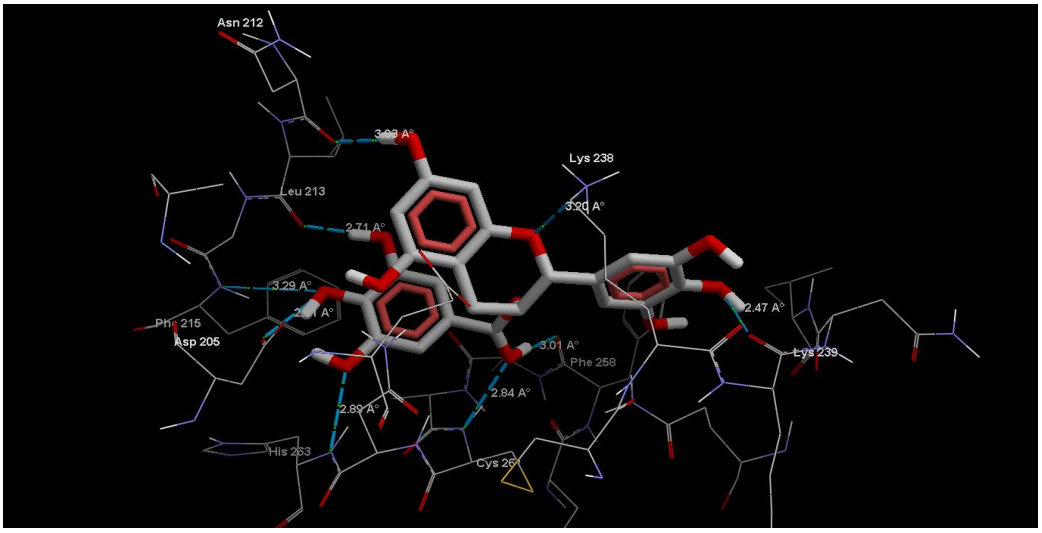


**Figure 8. Binding mode of EGCG into HPL, hydrogen bonding interactions are shown as green dotted lines.**

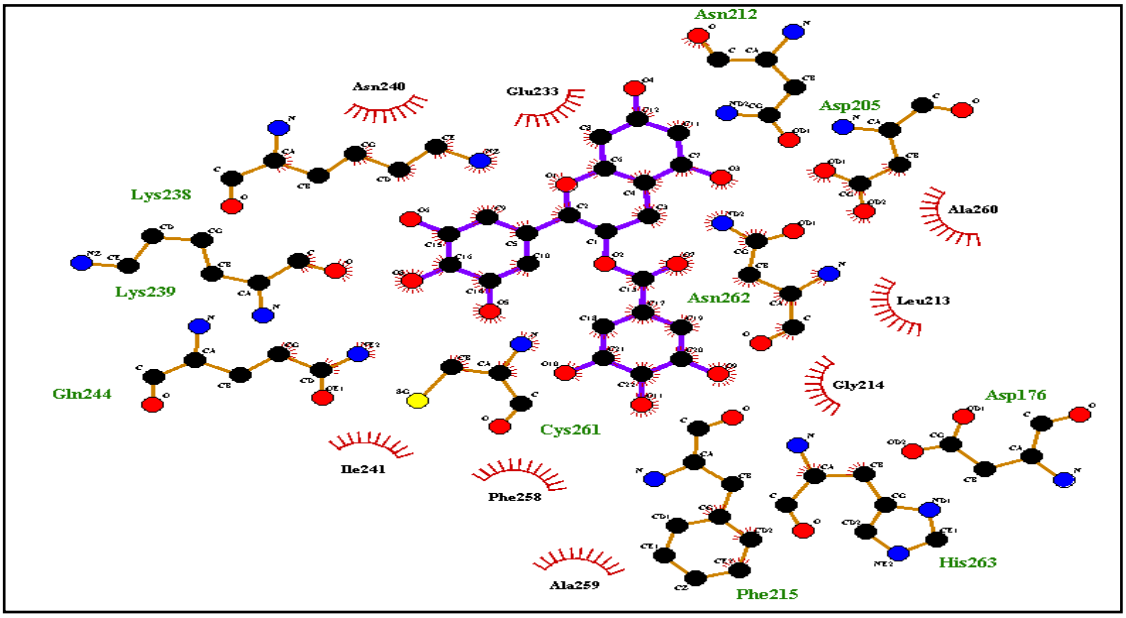


**Figure 9. Two dimensional representations of the best docking pose for (EGCG) inside HPL binding pocket**

**Comparison of interactions between EGCG-PPL and EGCG-HPL complexes**

We analyzed the pose solutions (conformation and orientation) of the EGCG ligand in the EGCG/1ETH and EGCG/1LPB complexes obtained with MVD docking simulations. In order to do so, we create surface type hydrophobicity for both complexes (Figure 10).

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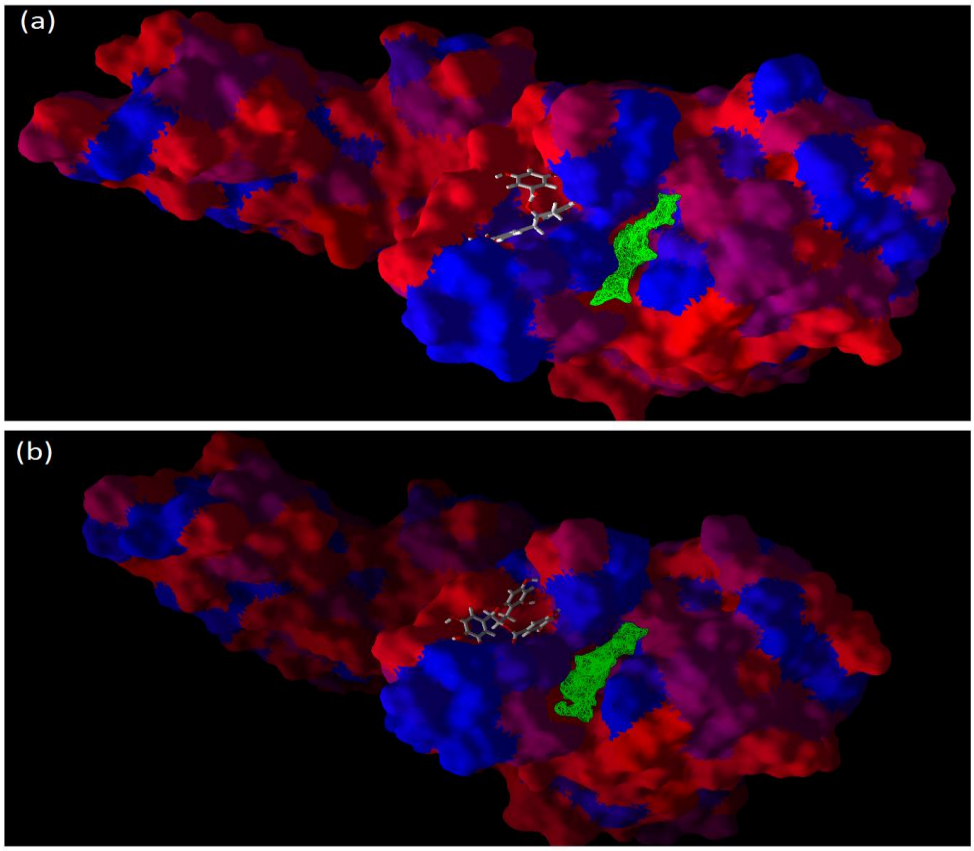


**Figure 10. Orientation of the EGCG ligand in the EGCG/1ETH (a) and EGCG/1LPB (b) complexes. The green grid represents the principal cavity.**

It is clearly visualized in figures (10) that the (−)-Epigallocatechin-3-gallate occupied the same bonding pocket (cavity 3) for both lipases, but here, the orientation is little different with an increase in the number of interactions between the EGCG and HPL.

In order to explain the relative orientations of the EGCG in the porcine and human-porcine complexes, we carried out a superposition studies.

The superimposition of the porcine Lipase on the human lipase is realized by RCSB PDB protein comparison tool using GCE Algorithm [27]. For the two lipases the superposition resulted in an RMSD of 0.8 Å indicating that they have very similar structures with percentage of 0.85 identity and 0.9 similarity, therefore the overall structure of porcine lipase closely resembles to the corresponding pancreas human (Figure 11). These results explain why the EGCG occupied the same pocket for the two Lipases.

The pocket 3 situated in The N-terminal domain is α/ß type; it comprises 200-270 residues. In this domain the sequence alignment of 1ETH.A.PDB and 1LPB.B.PDB (Figure 12) showed that the structurally is equivalent but some residues present significant differences (table 5), this rearrangement can probably alters the orientation of the ligand of inhibitor (EGCG). Hence, it can be concluded that several favorable interactions have been detected with Pancreatic Lipase Human better than with the Porcine Pancreatic Lipase. These interactions have positively contributed in the stability of the EGCG into the active site.

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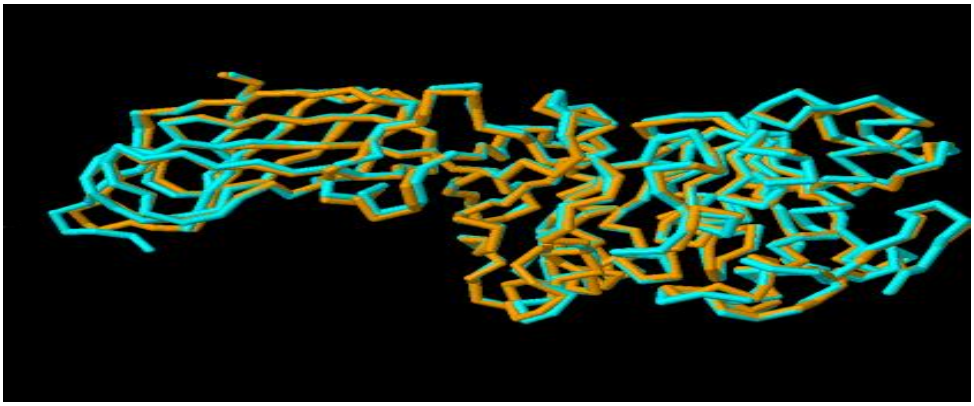

**Figure 11: Superimposition of the porcine lipase pancreas (orange) on the human lipase pancreas (cyan). The figure was made with the JSmol program.**

**Table 5. Residues of PPL and HPL in pocket 3, respectively.**

| Residues of PPL in the sequence alignment of 1ETH.A.PDB | Residues of HPL in the sequence alignment of 1LPB.B.PDB |
|---|---|
| Ala 207 | Gly206 |
| ILE 211 | Val 210 |
| THR 221 | Val 220 |
| Lys233 | Val 233 |
| Gln 234 | GLU 233 |
| Gln 239 | Lys 238 |
| Val 260 | ALA 259 |

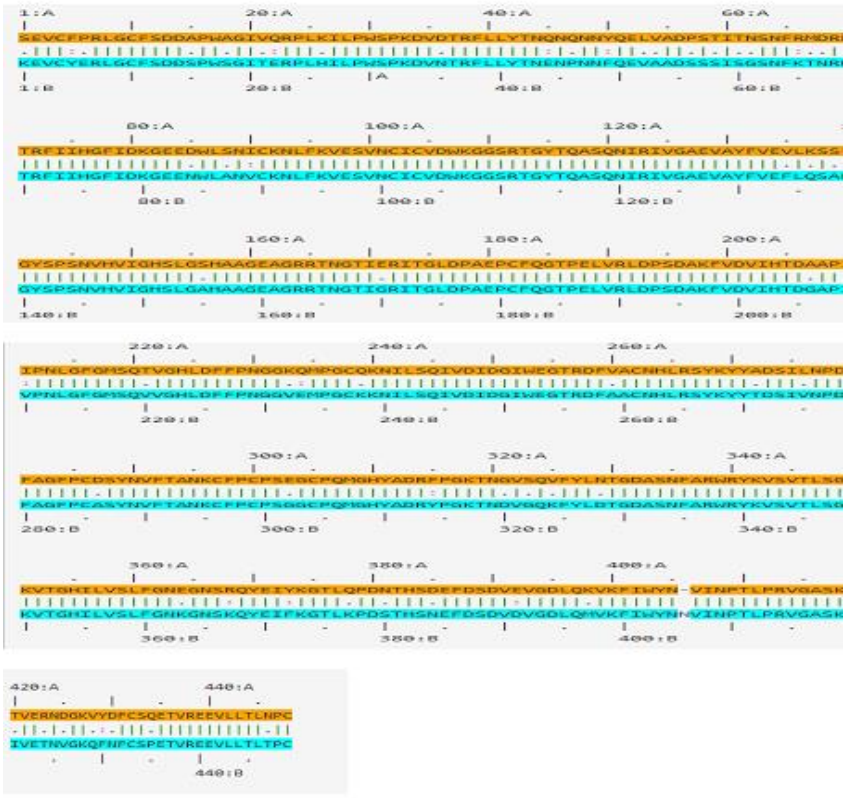

**Figure 12. Sequence alignment of 1ETH.A.PDB and 1LPB.B.PDB produced by JCE Algorithm. Structurally equivalent and identical residues, Structurally equivalent and similar residues, Structurally equivalent, but not similar residues.**

## CONCLUSION

In conclusion, we clarified in silico the mechanism of (−)-Epigallocatechin-3-gallate (EGCG) activity using a molecular docking studies, since this natural product is a non competitive PL inhibitor. The best docking solution was observed in cavity 3 situated in the vicinage of the site active, which showed a preferential binding mode. In this complex, some putative ligand/protein interactions were established, that deformer molecular conformation of lipase. Important hydrogen bonds have been formed with the residues His 263(PPL) and His 264(HPL), which are part of the catalytic triad of these enzymes. However, the galloyl group presents the key factor contributed to the enhancement of the number of interaction compared to other Catechin. An in silico comparative study between the interaction of EGCG-PPL and EGCG-HPL complexes showed that the Epigallocatechin-3-gallate (EGCG) has an inhibitory activity towards HPL better than PPL.

This work will provide a platform for the Characterization of Binding Interactions of the non-competitive type inhibitor using the molecular docking and could provide certain information about the inhibition mechanism of Catechin against other digestive lipase in order to discover a new potential inhibitors relevant to the treatment of Obesity disease.

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## REFERENCES

[1] Yun JW. Phytochemistry 2010; 71 (14-15): 1625-1641.
[2] Mohammad M, Al-masri IM, Issa A, Khdair A, Bustanji Y. Med Chem Res 2013; 22 (5), 2273-2278.
[3] Lunagariya NA, Patel NK, Jagtap SC, Bhutani KK. EXCLI Journal 2014; 13: 897-921.
[4] Liang LF, Wang T, Cai YS, He WF, Sun P, Li YF, Huang Q, Taglialatela-Scafati O, Wang HY, Guo YW. Eur J Med Chem 2014; 79: 290-297.
[5] Al-masri IM. Jordan Journal of Pharmaceutical Sciences 2013; 6 (3): 271-279.
[6] Wu X, He W, Zhang H, Li Y, Liu Z, He Z. Food Chem 2014; 142: 306-310.
[7] Birari RB, Bhutani KK. Drug Discov Today 2007; 12 (19-20):879-889.
[8] Larsen CA, Dashwood RH, Bisson WH. Pharmacol Res 2010; 62 (6): 457-464.
[9] Nguyen TT, Moon YH, Ryu YB, Kim YM, Nam SH, Kim MS, Kimura A, Kim D. Enzyme Microb Technol 2013; 52 (1): 26- 31.
[10] Sergent T, Vanderstraeten J, Winand J, Beguin P, Schneider YJ. Food Chem 2012; 135: 68-73.
[11] Wu X, He W, Yao L, Zhang H, Liu Z, Wang W, Ye Y, Cao J. J Agric Food Chem 2013; 61 (37): 8829-8835.
[12] Laskar MA, Duttachoudhury M. Res J Pharm Biol Chem Sci. 2014; 5 (6): 1109-1115.
[13] Veselinović JB, Veselinović AM, Nikolić GM, Pešić SZ, Stojanović DB, Matejić JS, Mihajilov-Krstev TM. Med Chem Res 2015; 24 (4):1626-1634.
[14] Liu L, Ma H, Yang N, Tang Y, Guo J, Tao W, Duan J. Thromb Res 2010; 126 (5): 365-378.
[15] Babu PA, Colluru VTSS, Anaparthy N. Comput Biol Med 2012; 42 (4): 446-457.
[16] Araújo JQ, Lima JA, Pinto Ada C, de Alencastro RB. J Mol Model 2011; 17 (6): 1401-1412.
[17] Gehlhaar DK, Verkhivker G, Rejto PA, Fogel DB, Fogel LJ, Freer ST. Proceedings of the fourth international conference on evolutionary programming, 1995, pp. 615-627.
[18] Gehlhaar DK, Bouzida D, Rejto PA. Proceedings of the seventh international conference on evolutionary programming, 1998, pp. 449-461.
[19] Yang JM, Chen CC. Proteins: Struct Funct Bioinf 2004; 55: 288-304.
[20] Torktaz I, Shahbani Zahiri H, Akbari Noghabi K. J Mol Graph Model 2013; 39:176-182.
[21] Torktaz I, Mohamadhashem F, Esmaeili A, Behjati M, Sharifzadeh S. BioImpacts 2013; 3 (3): 141-144.
[22] Babu RO, Moorkoth D, Azeez S, Eapen SJ. Bioinformation 2012; 8 (7): 319-325.
[23] Laskowski RA, Swindells MB. J Chem Inf Model 2011; 51 (10): 2778-2786.
[24] Wang S, Sun Z, Dong S, Liu Y, Liu Y. Plos One 2014; 9 (11): e111143.
[25] Gargouri Y, Ransac S, Verger R. Biochim Biophys Acta 1997; 1344 (1): 6-37.
[26] Aloulou A, Rodriguez JA. Biochim Biophys Acta 2006; 1761 (9):995-1013.
[27] Prlic A, Bliven S, Rose PW, Bluhm WF, Bizon C, Godzik A, Bourne PE. Bioinformatics 2010; 26 (23): 2983-2985.